Case Reports

Acute Pancreatitis Associated With High-Dose Interleukin-2 Immunotherapy for Malignant Melanoma

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THE LYMPHOKINE INTERLEUKIN 2 (IL-2) has significant antineoplastic activity against metastatic malignant melanomas and renal cell carcinomas. Objective responses have occurred in 20% to 33% of patients treated with high-dose IL-2 plus lymphokine-activated killer cells. Complete remissions have been obtained in about 8% to 15% of treated patients.[1,2] Most of the complete responses have lasted many months, with the longest approaching five years.[1] Unfortunately, the toxicity of IL-2 is substantial and can involve several organ systems. The various side effects of IL-2 have been extensively described by Rosenberg and colleagues.[1-4] Frequent side effects include a pronounced increase in vascular permeability, called the vascular leak syndrome, which is manifested by decreased intravascular volume and peripheral resistance and increases in interstitial fluid. This is clinically manifest by weight gain, edema, hypotension (often requiring pressor therapy), and oliguria. Other important side effects include fever, chills, anemia, and thrombocytopenia. Common toxic effects to the gastrointestinal system include nausea and vomiting, diarrhea, anorexia, elevated liver function tests, and, rarely, spontaneous bowel perforation (< 1% of treated patients).[5] Pancreatitis has not been previously reported with IL-2 therapy.

We describe two cases of probable pancreatitis associated with high-dose bolus IL-2 therapy and provide a brief discussion of the evidence for IL-2 as the etiologic agent.

Report of Cases

Case 1

The patient, a 63-year-old man, had metastatic melanoma to the right inguinal lymph nodes develop in August 1988. Pretherapy staging procedures showed a right inguinal mass and extensive right iliac and para-aortic adenopathy to the level of the diaphragm. There were no visceral metastases. The patient drank alcohol occasionally, consuming about 500 ml of alcohol per month. There was a more substantial history of alcohol consumption in the past. There was no history of previous abdominal operations, gallstones, pancreatitis, or hypertriglyceridemia. The patient was not receiving any medications before the IL-2 therapy.

In October 1988, the patient was treated on a multi-institutional protocol with the administration of high-dose bolus IL-2 without lymphokine-activated killer cells (following the written documentation of informed consent on an institutional review board-approved protocol). He received IL-2 at 100,000 units per kg (7.3×10^6 units) intravenously every eight hours for a total of 14 doses. Concomitant medications included acetaminophen, 650 mg every four hours; indomethacin, 50 mg every eight hours; and ranitidine, 150 mg twice a day. During the last six doses of IL-2 and during the following ten days, the patient received furosemide to relieve treatment-related weight gain. Oliguria did not develop (urine output < 240 ml during an eight-hour period) and neither did hypotension (systolic blood pressure < 90 torr) during IL-2 therapy.

Three days after the last dose of IL-2, fever and marked confusion developed. A computed tomographic (CT) scan of the head and the results of a lumbar puncture were normal. A chest x-ray film showed a left-sided pleural effusion. A thoracentesis established the exudative nature of the effusion. A pleural fluid amylase level was 87 IU per liter. A day later the patient complained of severe left upper quadrant pain. On physical examination his abdomen was distended and had rare bowel sounds. Supine and upright radiographs of the abdomen revealed an ileus with multiple air-fluid levels but no free air. A CT scan of the abdomen was without change from the pretreatment study. The pancreas did not appear edematous. There was no dilatation of the gallbladder or bile ducts, nor were gallstones visualized. A serum amylase level was 75 IU per liter (normal 23 to 185) and a lipase level was 250 IU per liter (normal 0 to 160). A simultaneous creatinine level was 122 μmol per liter (1.6 mg per dl; normal 61 to 107 μmol per liter). The amylase and lipase values increased over the four-day period following the last dose of IL-2 and peaked at 198 IU per liter and 470 IU per liter, respectively. By this time the creatinine level had declined to 84 μmol per liter (1.1 mg per dl). The episode of pancreatitis was treated with bowel rest and narcotics given intravenously with resolution of the abdominal pain three days after it began.

A posttreatment follow-up at two weeks revealed normal serum amylase and lipase values, and he had suffered no further bouts of abdominal pain. Nine weeks after the initiation of therapy, a partial response was documented. The patient refused further IL-2 therapy. His disease has currently stabilized at pretreatment dimensions.

Case 2

The patient, a 49-year-old man, was diagnosed to have malignant melanoma metastatic to the left axillary and inguinal lymph nodes. A pretherapy staging evaluation showed

(Birchfield GR, Ward JH, Redman BG, et al: Acute pancreatitis associated with high-dose interleukin-2 immunotherapy for malignant melanoma. West J Med 1990 Jun; 152:714-716)

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This work was supported by Veterans Administration Medical Research Funds, the Utah Regional Cancer Center Core grant No. CA42014, and Clinical Research Center grant No. RR00064 from the National Institutes of Health.

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ABBREVIATIONS USED IN TEXT
CT = computed tomography
IL-2 = interleukin 2

polycystic renal and hepatic disease but no visceral metastases. There was a history of alcohol abuse in the past, but no history of gallstones, pancreatitis, nor recent abdominal operations. He was taking acetaminophen and aspirin for pain.

In December 1988, the patient was started on a regimen of IL-2 at 100,000 units per kg given intravenously every eight hours (following written documentation of informed consent). Concomitant medications included indomethacin, 25 mg every 8 hours; acetaminophen, 650 mg every 4 hours; and ranitidine, 150 mg every 12 hours. Because of treatment-associated weight gain, furosemide administration was begun on day 5. The patient received all 14 planned doses of IL-2 without hypotension or oliguria.

One day following the last dose of IL-2, the patient began experiencing severe, diffuse abdominal pain, anorexia, nausea and vomiting, and decreased urinary output. An abdominal radiograph showed an ileus. Ultrasonography and CT scan of the abdomen showed an edematous pancreas with peripancreatic and left perirenal fluid. No evidence of gallbladder disease or biliary duct dilatation was seen. The serum amylase and lipase levels were elevated at 44 IU per liter (normal 30 to 110) and 9,633 IU per liter (normal 23 to 208), respectively. The serum creatinine level was 336 μmol per liter (4.4 mg per dl). As the creatinine level returned to normal, however, the posttreatment serum amylase and lipase levels continued to rise and peaked three days after the onset of pain at 484 and 13,286 IU per liter, respectively. The episode of pancreatitis was treated with bowel rest. Low doses of dopamine were given to treat the oliguria. The patient's symptoms resolved six days after the last dose of IL-2. Treatment with IL-2 was not repeated owing to disease progression.

Discussion

The diagnosis of acute pancreatitis is based primarily on clinical symptoms and signs, with confirmation by laboratory and radiographic studies.[6-8] The rapid onset of severe and constant abdominal pain, which may radiate to the back, is the classic clinical feature. The pain may last for hours to days. Ileus and pleural effusions are frequently associated clinical findings. Supporting laboratory data for the diagnosis of acute pancreatitis include an elevated serum amylase value, lipase level, or both, and the radiographic finding of an edematous pancreas by ultrasonogram or computed tomography. Conventional abdominal radiographs may also show pleural effusions (usually left-sided) and an ileus.

Symptoms and radiographic findings compatible with the diagnosis of pancreatitis developed in our patients shortly after the administration of IL-2. The first patient should be considered as having probable pancreatitis because of relatively minor elevations of serum amylase and lipase levels, as well as relatively modest pleural fluid amylase levels. This patient's symptoms and signs were compatible with the diagnosis, however, and no alternative explanation, such as bowel perforation or sepsis, could be found, despite an exhaustive evaluation. Our second patient had much more classic pancreatitis. These symptoms and signs were associated with significant elevations of serum amylase and lipase levels. Other common causes of acute pancreatitis, such as a recent abdominal operation, gallstones, hypertriglyceridemia, and malformations of the pancreas, were excluded in our patients. Hypotensive shock, a rare cause of acute pancreatitis, did not occur.[7,8] The elevated serum amylase and lipase values could not be explained on the basis of elevated serum creatinine values because they persisted well after the normalization of serum creatinine values in both patients.

Medications are important etiologic agents in the development of acute pancreatitis. Agents associated with the development of acute pancreatitis include furosemide, estrogens, thiazide diuretics, azathioprine, tetracycline, and sulfonamides. Less well-documented associations of glucocorticosteroids, indomethacin, acetaminophen, and cimetidine with the development of pancreatitis have also been reported.[6] It is possible to see elevated pancreatic enyzme levels and clinical pancreatitis as a protean manifestation of metastatic melanoma. Imaging studies of the abdomen were unable to detect pancreatic metastases in either patient, and subsequent clinical and radiographic observation make pancreatic metastases unlikely.

The time course of the development of the probable pancreatitis observed in our patients tentatively suggests that IL-2 may be either the etiologic or a contributory agent. Withdrawal of the drug coincided with the prompt resolution of symptoms and amylase and lipase elevations. Interleukin 2 is known to be a potent proinflammatory agent, the use of which can result in activation and increased cytotoxicity of lymphocytes.[9] In addition, this agent is known to cause the release of various inflammatory cytokines, such as interleukin 1, tumor necrosis factor, and interferons.[10] An exacerbation of damage to normal tissues in sites of preexisting inflammation has been described in an experimental model of viral myocarditis.[11] It is therefore reasonable to consider that the use of this cytokine might exacerbate chronic or subclinical pancreatic inflammation or might even trigger the injury and immune recognition of normal pancreatic cells.

A contribution of other agents to the development of pancreatitis in our patients cannot be excluded, as both received furosemide, indomethacin, and ranitidine during treatment. These agents may have additive or synergistic properties with IL-2 and could have contributed to the development of pancreatitis. It is interesting to note that both our patients had a previous history of substantial alcohol consumption, although neither had been drinking for a significant period (months to years) before the onset of pancreatitis. Whether previous pancreatic damage predisposes to an IL-2-mediated injury remains conjectural. In neither of our patients was IL-2 therapy readministered (because of refusal and a lack of response, respectively).

Two additional patients treated with IL-2 are known to have had asymptomatic pancreatic enzyme elevations develop (Michael Hawkins, MD, National Cancer Institute, Bethesda, Md, oral communication, May 1989). Three additional patients treated with IL-2 plus γ-interferon protocols have also had symptomatic pancreatitis develop (M. Hawkins, MD, oral communication and unpublished data, May 1989). These observations suggest that IL-2 treatment may play a role in the development of pancreatitis. The frequency of asymptomatic or symptomatic pancreatic inflammation appears to be very low, as this complication has been reported in less than 1% of patients treated with high-dose IL-2 therapy (more than 600 patients). One patient has been

rechallenged with an identical dose and schedule of IL-2 and γ-interferon without a recurrence of clinical symptoms and signs of pancreatitis or elevations of serum lipase or amylase levels (B.G.R., unpublished data, April 1989).

The acute onset of severe abdominal pain and ileus in patients treated with IL-2 is important because the possibility of spontaneous bowel perforation is a known complication.[5] Our experience, described herein, suggests the inclusion of acute pancreatitis in the differential diagnosis of acute abdominal pain in IL-2-treated patients. A careful physical examination and the appropriate laboratory and radiographic studies should be done to both diagnose acute pancreatitis and exclude spontaneous bowel perforation. Both of our patients responded to the cessation of IL-2 therapy and bowel rest as primary therapeutic maneuvers. We, therefore, recommend conservative therapy for the initial treatment of IL-2-associated pancreatitis. Whether pancreatitis will recur following the rechallenge of patients with IL-2-related pancreatitis with a further course of IL-2 therapy remains to be established.

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Rhabdomyolysis and *Staphylococcus aureus* Septicemia in a Man With the Acquired Immunodeficiency Syndrome

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MYALGIA IS A COMMON COMPLAINT among patients with the acquired immunodeficiency syndrome (AIDS), particularly those taking zidovudine.[1] Rhabdomyolysis, a clinical syndrome of skeletal muscle injury, is an uncommon but important cause of myalgia and has been associated with staphylococcal septicemia in three patients without AIDS.[2-4] Infection with *Staphylococcus aureus* has been noted with increased frequency in patients with AIDS.[5-7] We report the case of a man with AIDS in whom diffuse myalgia developed and who was found to have *S aureus* septicemia with nonsuppurative rhabdomyolysis.

Report of a Case

The patient, a 43-year-old homosexual man, had two previous episodes of *Pneumocystis carinii* pneumonia that were successfully treated with regimens of trimethoprim-sulfamethoxazole, pentamidine isethionate, and dapsone-trimethoprim. Eight months before admission, therapy with zidovudine, 250 mg every four hours, was started; after five months the dose was decreased to 100 mg every four hours because of transient granulocytopenia. Other medical problems included depression, recurrent herpes genitalis and labialis, oral candidiasis, and dermatitis.

Four weeks before admission, he received influenza and pneumococcal immunizations. One and a half weeks before admission, he had the development of a nonproductive cough, malaise, and intermittent fever and chills. Four days later he began to have diffuse myalgia and noted difficulty initiating urine flow, with frequency and malodorous, dark urine. He also had painful sores on his tongue and soft palate and diarrhea. Three days before admission a visiting nurse noted a temperature of 39.6°C (103.3°F) and normal findings on a chest examination. The day before admission his muscle pains had so increased that he would not get out of bed. He also had dyspnea on exertion. On the morning of admission he was incontinent of stool and began to hallucinate. At the time of admission his medications included acyclovir sodium, 200 mg five times a day; lorazepam, 2 mg twice a day; and amitriptyline hydrochloride, 75 mg at bedtime.

On physical examination he was drowsy but arousable, with a temperature of 34.4°C (93.9°F), a heart rate of 125 beats per minute, a respiratory rate of 60 per minute, and a systolic blood pressure of 70 mm of mercury. He had acrocyanosis, left-sided rales, diffuse weakness, and pronounced muscle tenderness of the arms and legs. He had no rash, muscle swelling, or cardiac murmurs; his neck was supple and his abdomen showed no abnormalities.

Laboratory tests elicited the following values: a hemoglobin level of 112 grams per liter; leukocyte count of 1.0×10^9 per liter with 0.05 segmented neutrophils, 0.15 band forms, 0.13 metamyelocytes, 0.01 myelocytes, 0.34 lymphocytes, 0.29 monocytes, and 0.03 eosinophils with toxic granulations and Döhle's bodies; and a platelet count of 103×10^9 per liter. The prothrombin time was 13.2 seconds with a control of 11.7 seconds, and a partial thromboplastin time was 30.2 seconds with a control of 26.1. Arterial blood gas determinations made while the patient was breathing room

(Wu AW, Benirschke K, McCutchan JA: Rhabdomyolysis and *Staphylococcus aureus* septicemia in a man with the acquired immunodeficiency syndrome. West J Med 1990 Jun; 152:716-719)

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